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| SHERIDAN ROSS PC 1560 BROADWAY SUITE 1200 DENVER, CO 80202 | | | EXAMINER ROONEY, NORA MAUREEN | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/808,846

Applicant(s)

GELFAND ET AL.

Examiner

NORA M. ROONEY

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-54 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36-54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-946)
- 3) ☒ Information Disclosure Statement(s) (PTO/SF/US)
Paper No(s)/Mail Date 03/18/2008
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/18/2008 has been entered.
2. Claims 36-54 are currently pending and under examination as they read on a method for reducing airway hyperresponsiveness by administering a phosphoantigen to a mammal.
3. Applicant's IDS document filed on 03/18/2008 is acknowledged.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
5. Claims 36-53 stand rejected and claim 54 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for : a method to reduce airway hyperresponsiveness in a mammal, consisting essentially of increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering TNF-alpha to the lung tissue of said mammal wherein

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administration of said TNF-alpha reduces airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered so that gamma delta T cells in the lung tissue of said mammal increases; wherein said TNF-alpha is administered so that gamma delta T cells in said mammal are activated; wherein said TNF-alpha is targeted to gamma delta T cells in the lung tissue of said mammal; wherein said TNF-alpha is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1; wherein said TNF-alpha is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes; wherein said TNF-alpha is administered to said mammal in an amount effective to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said TNF-alpha; wherein said TNF-alpha is administered with a pharmaceutically acceptable excipient; wherein said TNF-alpha is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha decreases airway methacholine responsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%; wherein increasing gamma delta T cell action by administration of said TNF-alpha improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as

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the PC_{20methacholine} FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma; does not reasonably provide enablement for a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering a **phosphoantigen** that activates gamma delta T cells to said mammal, wherein administration of said **phosphoantigen** reduces airway hyperresponsiveness in said mammal of claim 36; wherein the **phosphoantigen** comprises **isoprenylpyrophosphate (IPP)** of claim 37; wherein said **pyrophosphate** is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said **phosphoantigen** is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said **phosphoantigen** is targeted to gamma delta T cells in the lung tissue of said mammal of claim 40; wherein said **phosphoantigen** is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said **phosphoantigen** is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said **phosphoantigen** is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said **phosphoantigen** is administered with a pharmaceutically acceptable excipient of claim 44;

wherein said **phosphoantigen** is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said **phosphoantigen** is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said **phosphoantigen** is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** improves said mammal's $PC_{20\text{methacholine}}$ FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20\text{methacholine}}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim 50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml of claim 51; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma of claim 52 and wherein the mammal is a human of claim 54. The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation for the same reasons as set forth in the Office Action mailed on 11/21/2007.

Applicant's arguments and declaration submitted on 03/18/2008 have been fully considered, but are insufficient to overcome the enablement rejection.

Applicant argues that:

"As an initial matter, the Gelfand Declaration not only presented results concerning the effect of TNF-alpha on airway hyperresponsiveness, but also demonstrated that $\gamma\delta$ T cells were required for the effect (*e.g.*, TNF-alpha had no effect in $\gamma\delta$ depleted mice). Moreover, the results show that the deleterious effect of $\gamma\delta$ T cell depletion can be overcome by administering TNF-alpha to the mice. These results, taken together, suggest that TNF-alpha likely acts as a replacement for natural $\gamma\delta$ T cell cytokine secretion. Thus, one of skill in the art would clearly understand from these results that $\gamma\delta$ T cell activation plays a role in airway hyperresponsiveness, and agents that stimulate $\gamma\delta$ T cells to produce TNF-alpha would also be expected to reduce airway hyperresponsiveness.

In view of the arguments set forth in the Office Action, the Examiner's sole issue appears to be the contention that the specification does not teach one of skill in the art to substitute the administration of phosphoantigens for the administration of TNF-alpha in the claimed methods to reduce airway hyperresponsiveness. Applicants respectfully submit that the Examiner's contention is incorrect.

As elaborated in detail above, the specification expressly teaches methods to "reduce or prevent airway hyperresponsiveness (AHR) in an animal that has, or is at risk of developing, airway hyperresponsiveness, by increasing the action of $\gamma\delta$ T cells (*i.e.*, $\gamma\delta$ T lymphocytes) in the animal." Specification, page 10, lines 11-14. The specification further teaches that a variety of agents can be used to induce the recited increase in action of $\gamma\delta$ T cells.¹ *Id.* at page 25, lines 5-9. The Application then specifically teaches that phosphoantigens, including IPP, represent one group of agents that can be used to activate or increase the action of $\gamma\delta$ T cells. *Id.* at page 31, lines 21- 24. The publication of Tanaka et al., which discloses the ability of IPP and a related family of prenyl pyrophosphate derivatives to activate $\gamma\delta$ T cells, is also referenced to provide examples of phosphoantigens suitable for use in the present invention. *Id.*

Considering the explicit teachings set forth above, it is clear that the specification expressly discloses the administration of phosphoantigens to increase the action of $\gamma\delta$ T cells in an animal and thereby reduce airway hyperresponsiveness. Applicants submit that the Examiner is requesting that each recitation of "agents" suitable for use in the claimed methods be accompanied by a list of all previously mentioned agents. Satisfaction of the enablement requirement does not require such a rote recitation where the specification's teachings are clear. What matters is that one of skill in the art, upon reading the disclosure of the instant application, would immediately recognize that phosphoantigens are "agents" that may be substituted for TNF-alpha in the methods of the invention to reduce airway hyperresponsiveness. Indeed, one need not be a skilled artisan to realize this aspect of the invention.

If the Examiner is asserting that the express teachings of the specification are inoperable, Applicants submit that it was known in the art, as of the priority date of the instant application, that phosphoantigens in general, and IPP in particular, were capable of activating $\gamma\delta$ T cells. As mentioned above, the publication of Tanaka et al., referenced by the specification, discloses the activation of $\gamma\delta$ T cells by a family of phosphoantigens that includes IPP. The publication cited by the Examiner on page 18 of the Office Action (Burk et al., 1995) further demonstrates this principle. Burk et al. discloses six phosphoantigens, including IPP, that activate human $\gamma\delta$ T cells. These references establish that the skilled artisan was aware that phosphoantigens were capable of activating $\gamma\delta$ T cells as of the priority date of the present application.

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Moreover, the references previously cited by the Examiner to demonstrate that the claimed invention is inoperable teach that the opposite is true. Sicard et al. concludes that administration of a phosphoantigen, BrHPP, represents a promising immunotherapeutic strategy for the induction of systemic Th1 cytokines and massive expansion of $\gamma\delta$ T cell subsets (see, for example, Abstract). Cendron et al. also concludes that phosphoantigen administration triggered immediate $\gamma\delta$ T cell activation and strong release of Th1 cytokines, while noting delayed responses to subsequent challenges in their model system (see page 561, col. 2).

Further, Applicants submit herewith the Declaration under 37 C.F.R. § 1.132 of Catherine Laplace as evidence that phosphoantigens can be used to reduce airway hyperresponsiveness in mammals according to the claimed methods. As set forth in the Declaration, three phosphoantigens, including IPP, BrHPP and a proprietary phosphoantigen termed "Compound X" activated human $\gamma\delta$ T cells and induced their production of TNF- α . These data are consistent with the art-recognized principle that phosphoantigens are capable of activating $\gamma\delta$ T cells.

The Declaration then describes an experiment assessing the effect of phosphoantigen treatment on early airway responses to inhaled allergen in rhesus macaque monkeys. The results of this experiment indicate that when monkeys are treated with a phosphoantigen according to the methods of the present invention, a statistically significant reduction in airway hyperresponsiveness is observed. The results also suggest that, in a non-human primate model system, phosphoantigen treatment may lead to a commensurate reduction in airway hyperresponsiveness-related diseases such as COPD. Taken together, the experiments demonstrate that administering a phosphoantigen that activates $\gamma\delta$ T cells to a mammal reduces airway hyperresponsiveness in the mammal, as recited in the instant claims.

Compound X is a phosphoantigen and has a structure quite similar to IPP. In particular, both compound X and IPP contain two phosphate groups positioned on the same end of the molecule. Likewise, Compound X and IPP share a similar carbon backbone structure and both exhibit a low molecular weight. These shared structural characteristics are exactly the same as those known in the art to be essential for $\gamma\delta$ T cell-stimulating activity at the time of invention, as demonstrated by the teachings of Burk et al., the very publication cited by the Examiner to demonstrate the level of phosphoantigen knowledge in the art at this time. Post-filing publications further confirm the structure-function relationship disclosed in Burk et al.² Thus, the results presented in the Laplace Declaration demonstrate that administering a phosphoantigen with a core structure known in the art at the time of invention to activate $\gamma\delta$ T cells reduces airway hyperresponsiveness in a mammal, as recited in the instant claims."

The LaPlace declaration filed on 03/18/2008 states:

"Sir:

I, Catherine Laplace, BSc., hereby declare as follows:

1. I am currently employed by Innate Pharma, S.A as a Research and Development Engineer and have held this position since 2000. During my work at Innate Pharma, I have subcontracted a study (with scientists of the California National Primate Research Center (CNPRC) at a UC Davis university who have developed a non-human primate model of asthma) to conduct experiments assessing the action of $\gamma\delta$ T cells in airway illnesses.

2. It is my understanding that Innate Pharma, S.A. is a licensee of the above-identified patent application:

3. This Declaration is being submitted in conjunction with an Amendment and Response to an Office Action having a mailing date of November 21, 2007, in the above-identified application.

4. I have reviewed, and I am familiar with, the above-identified application and the presently pending claims, and I have also reviewed documents from the file history of this application, including the Office Action mailed November 21, 2007. The following discussion pertains to the Examiner's rejection of

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Claims 36-53 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. In particular, the following discussion addresses the Examiner's argument that the specification does not enable the invention that is claimed.

5. It is my understanding that the Examiner's contends that the specification does not teach one skilled in the art a method for reducing airway hyperresponsiveness in a mammal by administering a phosphoantigen. The experiments set forth in the Appendices below were conducted to assess the effect of phosphoantigen treatment on early airway responses to inhaled allergen in rhesus macaque monkeys. The phosphoantigen administered is referred to as "compound X."

Appendix A describes the experimental protocol used. As described in the Examples of the above-identified application, animals were sensitized by exposure to an allergen (along with non-sensitized Controls) followed by repeated aerosol challenge with the same allergen and an assessment of airway responsiveness in each animal.

Appendix B shows the early resistance in three macaque groups: one group non-sensitized; another HDMA-sensitized and the final group HDMA-sensitized and administered compound X prior to a second HDMA challenge. All macaques were challenged twice. In the HDMA sensitized and compound X treated macaques, the first challenge occurs before the administration of a compound X and the second challenge takes place when the monkey is treated by compound X.

The data presented in Appendix B demonstrate a reduction in airway hyperresponsiveness in monkeys upon administering a phosphoantigen. As can be established from the figure in Appendix B, the phosphoantigen-treated sensitized animal (open dots) experienced a decrease of 43% in early airway response, where the untreated sensitized animal (solid squares) experienced a significantly lower decrease (17%). No airway response to the inhalation of allergen was observed in the non-sensitized control monkey (solid triangles). Additionally, the report handled by the subcontractor to accompany these data states: "In monkey treated with the phosphoantigen, there was a decrease in the early airway response. [...] While limited, the data would suggest that the phosphoantigen treatment attenuates early airway responses to inhaled allergen." The data therefore tend to show a reduction of AHR diseases i.e. COPD in a non-human primate model.

The complete formula of compound X is not shown due to confidentiality reasons. However, compound X is a phosphoantigen, and, as shown in Appendix C, has a structure quite similar to IPP. In particular, both compound X and IPP contain two phosphate groups positioned on the same end of the molecule. Likewise, compound X and IPP share a similar carbon backbone structure and are similar in molecular weight.

Appendix D describes a protocol used to assess the amount of TNF α released by $\gamma\delta$ T cells following stimulation with a phosphoantigen. Using this protocol, $\gamma\delta$ T cells were stimulated with one of the following phosphoantigens: compound X, IPP or BrHPP and the amount of TNF α released determined. The ECS0 was then calculated for each compound. As shown in the figure of Appendix E, compound X, BrHPP and IPP are each able to stimulate $\gamma\delta$ T cells. This stimulation of $\gamma\delta$ T cells by compound X (or with IPP or BrHPP) results in the release of TNF α , as described in the above-referenced patent application."

It remains the Examiner's position that those skilled in the art could not extrapolate the disclosure of the specification into a method to reduce airway hyperresponsiveness in a mammal by administering any phosphoantigen. The La Place declaration which demonstrates the

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administration of one non-disclosed proprietary phosphoantigen "compound X" to treat hyperresponsiveness is not sufficient to establish that the genus of all phosphoantigen compounds could be used to reduce airway hyperresponsiveness in a mammal that has or is at risk of developing a respiratory condition associated with airway hyperresponsiveness to overcome the instant rejection. The art shows that "both the number and position of the phosphate groups, as well as the residues connected with the carbon backbone are required for stimulation" of $\gamma\delta$ T cells. (In particular, Burk et al., PTO-892 mailed 11/21/2007, Reference U, abstract, whole document). In addition, the 2006 post-filing date art of Zhang et al. teaches that the structure of well-known, previously reported phosphoantigens is not correct (PTO-892, Reference U; In particular, whole document). On page 985, Zhang et al. teaches that "There are, however, many questions as to the mechanism of action of phosphoantigens, as well as to their chemical structures." The art of Zhang et al. combined with the art of Burk et al. teaches that those of ordinary skill in the art do not know what phosphoantigen structures correlate with in vitro gamma delta T cell activation, much less in vivo gamma delta T cell activation that increases TNF-alpha and leads to reduced airway hyperresponsiveness. Neither the specification nor the state of the art at the time of invention provides adequate guidance and support regarding which phosphoantigens can be used in the reduce airway hyperresponsiveness to enable the instant claims. Therefore, those skilled in the art at the time of the invention would not know to use IPP or any phosphoantigen in general to perform the recited method.

6. Claims 36-53 stand rejected and claim 54 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

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way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a method to reduce airway hyperresponsiveness in a mammal, consisting essentially of increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering TNF-alpha to the lung tissue of said mammal wherein administration of said TNF-alpha reduces airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered so that gamma delta T cells in the lung tissue of said mammal increases; wherein said TNF-alpha is administered so that gamma delta T cells in said mammal are activated; wherein said TNF-alpha is targeted to gamma delta T cells in the lung tissue of said mammal; wherein said TNF-alpha is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1; wherein said TNF-alpha is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes; wherein said TNF-alpha is administered to said mammal in an amount effective to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said TNF-alpha; wherein said TNF-alpha is administered with a pharmaceutically acceptable excipient; wherein said TNF-alpha is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal; wherein said TNF-alpha is administered prior to development of airway hyperresponsiveness in said mammal; wherein

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increasing gamma delta T cell action by administration of said TNF-alpha decreases airway methacholine responsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said TNF-alpha reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%; wherein increasing gamma delta T cell action by administration of said TNF-alpha improves said mammal's $PC_{20\text{methacholine}}$ FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the $PC_{20\text{methacholine}}$ FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma.

Applicant is not in possession of : a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering a **phosphoantigen** that activates gamma delta T cells to said mammal, wherein administration of said **phosphoantigen** reduces airway hyperresponsiveness in said mammal of claim 36; wherein the **phosphoantigen** comprises **isoprenylpyrophosphate (IPP)** of claim 37; wherein said **pyrophosphate** is administered so that gamma delta T cells in the lung tissue of said mammal increases of claim 38; wherein said **phosphoantigen** is administered so that gamma delta T cells in said mammal are activated of claim 39; wherein said **phosphoantigen** is targeted to gamma

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delta T cells in the lung tissue of said mammal of claim 40; wherein said **phosphoantigen** is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1 of claim 41; wherein said **phosphoantigen** is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes of claim 42; wherein said **phosphoantigen** is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen of claim 43; wherein said **phosphoantigen** is administered with a pharmaceutically acceptable excipient of claim 44; wherein said **phosphoantigen** is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 45; wherein said **phosphoantigen** is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal of claim 46; wherein said **phosphoantigen** is administered prior to development of airway hyperresponsiveness in said mammal; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** decreases airway methacholine responsiveness in said mammal of claim 48; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5% of claim 49; wherein increasing gamma delta T cell action by administration of said **phosphoantigen** improves said mammal's PC_{20methacholine} FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the PC_{20methacholine} FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine of claim

50; wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml of claim 51; wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma of claim 52; and wherein the mammal is a human of claim 54 for the same reasons as set forth in the Office Action mailed on 11/21/2007.

Applicant's arguments filed on 03/18/2008 have been fully considered, but are not found persuasive.

Applicant argues:

" Applicants respectfully traverse these rejections. However, in an effort to clarify the invention and to expedite prosecution, Applicants have amended claims 36 and 53 to recite the administration of a phosphoantigen that activates $\gamma\delta$ T cells. Applicants submit that one of skill in the art, using the teachings of the instant specification and the knowledge in the art at the time of filing, would immediately understand that Applicants were in possession of the full scope of the claimed invention.

The written description requirement is satisfied if the specification discloses the invention in sufficient detail to allow a person skilled in the art to reasonably conclude that the inventor had possession of the invention as claimed. M.P.E.P. § 2163. While claims drawn to a genus may be adequately supported by the disclosure of a representative number of species within the genus, the Federal Circuit has made clear that the specification need not describe every permutation of an invention nor subject matter known to those of skill in the art. *Capon v. Eshhar*, 418 F.3d 1349, 1359-60 (Fed. Cir. 2005). Moreover, an adequate written description of an invention that involves biological macromolecules need not contain a recitation of each known structure, particularly when those structures are already known in the art. *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) ("the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly, we hold that where..., accessible literature sources clearly provided, as of the relevant date, [the sequences], satisfaction of the written description requirement does not require either the recitation or incorporation by reference").

The claims, as amended, recite phosphoantigens that activate $\gamma\delta$ T cells rather than all known phosphoantigens. As previously discussed in the response to the Office Action dated May 3, 2007, the term phosphoantigen was well known to those of skill in the art at the time of the invention (see previously submitted references Belmont et al. and Espinosa et al.) These references, along with the publication of Tanaka et al., referenced by the specification, also establish that at the time of the invention, it was known that phosphoantigens could activate $\gamma\delta$ T cells.

Moreover, one of skill in the art also knew, at the time of invention, numerous examples of phosphoantigens capable of activating $\gamma\delta$ T cells, including detailed structural information on what aspects of the phosphoantigens contributed to the ability to activate the cells. Tanaka et al., for example, discloses a family of phosphoantigen compounds (prenyl pyrophosphate derivatives), including IPP, that activate $\gamma\delta$ T cells and demonstrates structural aspects of these compounds that are responsible for the activation (see

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Abstract: "Substitution of phosphate for the pyrophosphate moiety, or elimination of the double bond, greatly reduced antigenic activity of the compounds.") Similarly, Constant et al., *Science* 264:267-270 (1994), teaches a family of γ -derivatives of uridine triphosphate (X- γ UTP) and thymidine triphosphate (X- γ TTP) that activate $\gamma\delta$ T cells.

Additional evidence showing that the structural aspects of phosphoantigens that contribute to the activation of $\gamma\delta$ T cells was known in the art at the time of invention is provided by the teachings of Burk et al. The experiments and results described in Burk et al. provide detailed structural data on phosphoantigens that activate $\gamma\delta$ T cells, including the position of the phosphate moiety, the number and localization of the phosphate groups, the nature of the residues connected to the carbon backbone, and the molecular mass of the phosphoantigens.³ Indeed, the Examiner acknowledges these teachings by quoting Burk et al. to establish that "the art shows that 'both the number and position of the phosphate groups, as well as the residues connected with the carbon backbone are required for stimulation' of $\gamma\delta$ T cells." Office Action, page 18. As with Tanaka et al. and Constant et al. discussed above, Burk et al. was published before the earliest priority date of the instant application.

Despite the Examiner's recognition of the knowledge in the art, the Examiner contends that the specification fails to provide support for the pending claims because it does not provide the very structural features of phosphoantigens described in references such as Burk et al. Applicants submit that the Examiner is improperly requiring that the specification include subject matter well known in the art and a description of each and every embodiment that may fall within the scope of the claims. Such a requirement is clearly contrary to what is needed to satisfy the written description requirement, as explained in the Federal Circuit's *Capon* and *Falkner* decisions.

Compliance with the written description requirement is assessed from the viewpoint of one skilled in the art, taking into account subject matter known in the field of invention. *\$3, Inc. v. Nvidia Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001). Considering the knowledge in the art at the time of filing, in particular the knowledge of the activation of $\gamma\delta$ T cells by phosphoantigens having defined structural characteristics, one of skill in the art, upon reading the instant specification, would immediately understand that Applicants were in possession of the full scope of the claimed invention. To require the disclosure of material well known in the art at the time of the invention would serve only to add "unnecessary bulk" to the specification."

The LaPlace declaration filed on 03/18/2008 states:

"Sir:

I, Catherine Laplace, BSc., hereby declare as follows:

1. I am currently employed by Innate Pharma, S.A as a Research and Development Engineer and have held this position since 2000. During my work at Innate Pharma, I have subcontracted a study (with scientists of the California National Primate Research Center (CNPRC) at a UC Davis university who have developed a non-human primate model of asthma) to conduct experiments assessing the action of $\gamma\delta$ T cells in airway illnesses.

2. It is my understanding that Innate Pharma, S.A. is a licensee of the above-identified patent application:

3. This Declaration is being submitted in conjunction with an Amendment and Response to an Office Action having a mailing date of November 21, 2007, in the above-identified application.

4. I have reviewed, and I am familiar with, the above-identified application and the presently pending claims, and I have also reviewed documents from the file history of this application, including the Office Action mailed November 21, 2007. The following discussion pertains to the Examiner's rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. In particular, the following

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discussion addresses the Examiner's argument that the specification does not enable the invention that is claimed.

5. It is my understanding that the Examiner's contends that the specification does not teach one skilled in the art a method for reducing airway hyperresponsiveness in a mammal by administering a phosphoantigen. The experiments set forth in the Appendices below were conducted to assess the effect of phosphoantigen treatment on early airway responses to inhaled allergen in rhesus macaque monkeys. The phosphoantigen administered is referred to as "compound X."

Appendix A describes the experimental protocol used. As described in the Examples of the above-identified application, animals were sensitized by exposure to an allergen (along with non-sensitized Controls) followed by repeated aerosol challenge with the same allergen and an assessment of airway responsiveness in each animal.

Appendix B shows the early resistance in three macaque groups: one group non-sensitized; another HDMA-sensitized and the final group HDMA-sensitized and administered compound X prior to a second HDMA challenge. All macaques were challenged twice. In the HDMA sensitized and compound X treated macaques, the first challenge occurs before the administration of a compound X and the second challenge takes place when the monkey is treated by compound X.

The data presented in Appendix B demonstrate a reduction in airway hyperresponsiveness in monkeys upon administering a phosphoantigen. As can be established from the figure in Appendix B, the phosphoantigen-treated sensitized animal (open dots) experienced a decrease of 43% in early airway response, where the untreated sensitized animal (solid squares) experienced a significantly lower decrease (17%). No airway response to the inhalation of allergen was observed in the non-sensitized control monkey (solid triangles). Additionally, the report handled by the subcontractor to accompany these data states: "In monkey treated with the phosphoantigen, there was a decrease in the early airway response. [...] While limited, the data would suggest that the phosphoantigen treatment attenuates early airway responses to inhaled allergen." The data therefore tend to show a reduction of AHR diseases i.e. COPD in a non-human primate model.

The complete formula of compound X is not shown due to confidentiality reasons. However, compound X is a phosphoantigen, and, as shown in Appendix C, has a structure quite similar to IPP. In particular, both compound X and IPP contain two phosphate groups positioned on the same end of the molecule. Likewise, compound X and IPP share a similar carbon backbone structure and are similar in molecular weight.

Appendix D describes a protocol used to assess the amount of TNF α released by $\gamma\delta$ T cells following stimulation with a phosphoantigen. Using this protocol, $\gamma\delta$ T cells were stimulated with one of the following phosphoantigens: compound X, IPP or BrHPP and the amount of TNF α released determined. The EC50 was then calculated for each compound. As shown in the figure of Appendix E, compound X, BrHPP and IPP are each able to stimulate $\gamma\delta$ T cells. This stimulation of $\gamma\delta$ T cells by compound X (or with IPP or BrHPP) results in the release of TNF α , as described in the above-referenced patent application."

It is the Examiner's position that the specification has not adequately described a correlation between function (reduces airway hyperresponsiveness) and phosphoantigen structure responsible for reducing airway hyperresponsiveness such that one of ordinary skill in the art would have known which phosphoantigens could be used to generate the disclosed function of

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reducing airway hyperresponsiveness in a mammal. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895. "Without a correlation between structure and function, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement." Ex parte Kubin, 83 U.S.P.Q.2d 1410 (BPAI 2007). The specification does not adequately describe the genus of all phosphoantigen non-peptide compounds for use in the claimed invention.

Contrary to Applicant's assertion, one of ordinary skill in the art would not be able to determine which phosphoantigens would work in the claimed invention since neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus of phosphoantigens that would work to reduce airway hyperresponsiveness in the claimed invention. The art shows that "both the number and position of the phosphate groups, as well as the residues connected with the carbon backbone are required for stimulation" of $\gamma\delta$ T cells. (In particular, Burk et al., PTO-892 mailed 11/21/2007, Reference U, abstract, whole document). In addition the 2006 post-filing date art of Zhang et al. teaches that the structure of well-known, previously reported phosphoantigens is not correct (PTO-892, Reference U; In particular, whole document). On page 985, Zhang et al. teaches that "There are, however, many questions as to the mechanism of action of phosphoantigens, as well as to their chemical structures." The art of Zhang et al. combined with the art of Burk et al. teaches that those of ordinary skill in the art do not know what

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phosphoantigen structures correlate with in vitro gamma delta T cell activation, much less in vivo gamma delta T cell activation that increases TNF-alpha and leads to reduced airway hyperresponsiveness. Applicant's assertion that all phosphoantigens would work is not supported by examples, description in the specification or the state of the art. No such structure requisite structure has been described in the specification.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 36-54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4, 18-19, 23-33, 36 and 38-39 of U.S. Patent No. 6,737,398 (the '398 patent).

Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 36-37 and 53 of the instant application and claims 1, 36, and 38-39 of the '398 patent are directed to a method to reduce airway hyperresponsiveness in a mammal, comprising increasing gamma delta T cell action in a mammal that has, or is at risk of developing, a respiratory condition associated with airway hyperresponsiveness by administering a phosphoantigen to administer TNF alpha that activates gamma delta T cells to said mammal, wherein administration of said phosphoantigen reduces airway hyperresponsiveness in said mammal;

Claims 38 of the instant application and claim 2 of the '398 patent are directed to wherein gamma delta T cells in the lung tissue of said mammal increases;

Claims 39 of the instant application and Claims 4 of the '398 patent are directed to wherein gamma delta T cells in said mammal are activated;

Claim 40 of the instant application and claim 18 of the '398 patent are directed to wherein said phosphoantigen to administer TNF alpha is targeted to gamma delta T cells in the lung tissue of said mammal;

Claim 41 of the instant application and claim 19 of the '398 patent are directed to wherein said phosphoantigen to administer TNF alpha is targeted to gamma delta T cells having T cell receptor selected from the group consisting of a murine TCR comprising Vgamma4 and a human TCR comprising Vgamma1;

Claim 42 of the instant application and claim 23 of the '398 patent are directed to wherein said phosphoantigen to administer TNF alpha is administered by a route selected from the group consisting of inhaled, intratracheal and nasal routes;

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Claim 43 of the instant application and claim 24 of the '398 patent are directed to wherein said phosphoantigen to administer TNF alpha is administered to said mammal in an amount effecting to reduce airway hyperresponsiveness in said mammal as compared to prior to administration of said phosphoantigen;

Claim 44 of the instant application and claim 25 of the '398 patent are directed to wherein said phosphoantigen to administer TNF alpha is administered with a pharmaceutically acceptable excipient;

Claim 45 of the instant application and claim 26 of the '398 patent are directed to wherein said phosphoantigen to administer TNF alpha is administered within between 1 hour and 6 days of an initial diagnosis of airway hyperresponsiveness in said mammal;

Claim 46 of the instant application and claim 27 of the '398 patent are directed to wherein said phosphoantigen to administer TNF alpha is administered within less than about 72 hours of an initial diagnosis of airway hyperresponsiveness in said mammal;

Claim 47 of the instant application and claim 28 of the '398 patent are directed to wherein said phosphoantigen to administer TNF alpha is administered prior to development of airway hyperresponsiveness in said mammal;

Claim 48 of the instant application and claim 29 of the '398 patent are directed to wherein increasing gamma delta T cell action by administration of said phosphoantigen to administer TNF alpha decreases airway methacholine responsiveness in said mammal;

Claim 49 of the instant application and claim 30 of the '398 patent are directed to wherein increasing gamma delta T cell action by administration of said phosphoantigen to administer

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TNF alpha reduces airway hyperresponsiveness of said mammal such that the FEV1 value of said mammal is improved by at least about 5%;

Claim 50 of the instant application and claim 31 of the '398 patent are directed to wherein increasing gamma delta T cell action by administration of said phosphoantigen to administer TNF alpha improves said mammal's PC20methacholine FEVt value obtained before increasing gamma delta T cell action when the mammal is provoked with a first concentration of methacholine is substantially the same as the PC20methacholine FEVt value obtained after increasing gamma delta T cell action when the mammal is provoked with double the amount of the first concentration of methacholine;

Claim 51 of the instant application and claim 32 of the '398 patent is directed to wherein said first concentration of methacholine is between about 0.01 mg/ml and about 8 mg/ml;

Claim 52 of the instant application and claim 33 of the '398 patent are directed to wherein said airway hyperresponsiveness is associated with a disease selected from the group consisting of chronic obstructive disease of the airways and asthma.

It would have been obvious to one of ordinary skill in the art at the time of invention to administer TNF-alpha by administering phosphoantigen to the mammal because they one of ordinary skill in the art at the time of invention from reading the disclosure of the '398 patent (which is the same as the instant specification) would "immediately recognize that phosphoantigens are "agents" that may be substituted for TNF-alpha in the methods of the invention to reduce airway hyperresponsiveness." (Applicant's response filed on 03/18/2008 page 8, lines 13-17).

Claim 54 of the instant application is directed to wherein the mammal is a human. It would have been obvious to one of ordinary skill in the art at the time of invention to reduce airway hyperresponsiveness in humans, given that the '398 patent teaches in column 25, lines 50-56 that the method can be performed in any animal, including humans.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 3, 2008

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Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600

/Eileen B. O'Hara/

Supervisory Patent Examiner

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